Office Action Summary	Application No.	Applicant(s)
	10/589,726	HAWIGER ET AL.
	Examiner	Art Unit
	Bridget E. Bunner	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 21-31* is/are pending in the application.

4a) Of the above claim(s) *15,26 and 29-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-14,16-19,21-25,27 and 28* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☒ Claim(s) *1-19 and 21-31* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 16 February 2011 has been entered.

Status of Application, Amendments and/or Claims

The amendment of 16 February 2011 has been entered in full. Claims 5-7, 12, 23, are amended. Claim 20 is cancelled.

Claims 15, 26, 29-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04 September 2009.

Claims 1-14, 16-19, 21-25, and 27-28 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to claim 7 at page 3 of the previous Office Action (16 August 2010) is *withdrawn* in view of the amended claim (16 February 2011).

2. The rejection of claim 5 under 35 U.S.C. 112, second paragraph, as set forth at pages 3-4 of the previous Office Action (16 August 2010) is *withdrawn* in view of the amended claim (16 February 2011).

3. The rejection of claim 7 under 35 U.S.C. § 112, first paragraph, as set forth at pages 4-12 of the previous Office Action (16 August 2010) is *withdrawn* in view of the amended claim (16 February 2011).

Claim Objections

4. Claims 6, 15 are objected to because of the following informalities:

4a. In claim 6, line 3, after the term "translocating", the word "sequence" should be inserted.

4b. Claim 15 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 12-14, 16-19, 21-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating an inflammatory disease in a subject suffering from said inflammatory disease comprising administering a polypeptide comprising a SOCS1 or SOCS3 sequence and a membrane translocation sequence to the subject, ***does not reasonably provide enablement for*** a method of treating an inflammatory disease in a subject wherein the subject is at risk for presenting with an inflammatory disease. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 12 is directed to a method of treating an inflammatory disease in a subject comprising administering a polypeptide comprising a suppressor of cytokine signaling 1 or 3 (SOCS1; SOCS3) sequence and a membrane translocating sequence at either amino or carboxy terminal end of the SOCS sequence to a subject. Claim 13 recites that the subject is a subject with an inflammatory disease or at risk for presenting with an inflammatory disease. Claim 23 recites a method of treating an inflammatory disease in a patient comprising administering an isolated polypeptide comprising a cell penetrating suppressor of cytokine signaling 1 or 3 (CP-SOCS1; CP-SOCS3) polypeptide to a patient. Claim 24 recites that the patient is presenting with an inflammatory disease or at risk for presenting with an inflammatory disease.

The specification of the instant application teaches that recombinant CP-SOCS3 suppresses systemic inflammation (pages 49-50, Example 4). The state of the art teaches that expression of SOCS1 or SOCS3 reduce inflammation in several different inflammatory diseases (Alexander et al. Annu Rev Immunol 22: 503-529, 2004; see especially page 519;; cited on the IDS of 28 April 2008; see also Hanada et al. Rev Physiol Biochem Pharmacol 149: 72-86, 2003, especially pages 77-80). The specification teaches that the compositions that inhibit cytokine-induced signaling disclosed can be administered prophylactically to patients or subjects who are at risk for inflammation or who have been newly exposed to an inflammation inducing substance, such as bacteria (page 32, lines 2527). Claims 13 and 24 specifically recite that the subject is at risk for presenting with an inflammatory disease.

Thus, the Examiner has interpreted the claims as not only encompassing treatment of an

inflammatory disease in a subject suffering from said disease, but also prophylactic treatment of an inflammatory disease in a subject who is at risk for inflammation or who has been newly exposed to an inflammation inducing substance. However, the specification does not disclose any methods or working examples for prophylaxis or "prevention" of an inflammatory disease in a subject, as required by claims 12-14, 16-19 and 21-25. A large quantity of experimentation would also be required of the skilled artisan to identify subjects who are at risk for presenting with an inflammatory disease. Such experimentation is considered undue. The limited guidance in the specification is not adequate and is merely an invitation for the skilled artisan to use the current invention as a starting point for further experimentation. The claimed method may not necessarily prevent an inflammatory disease in subject by administering an isolated polypeptide comprising a SOCS sequence and a membrane translocating sequence. The skilled artisan must resort to trial and error experimentation to determine the optimal dosage, duration, and mode of administration the polypeptide. Such trial and error experimentation is considered undue. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed."

Due to the large quantity of experimentation necessary to determine the optimal quantity, duration, and route of administration of the cell penetrating SOCS1 or SOCS3 polypeptide to prophylactically treat or prevent an inflammatory disease; the lack of direction/guidance presented in the specification regarding such; the absence of working examples; the complex nature of the invention; and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-4, 6-11, 27, 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hilton et al. (U.S. Patent 6,323,317) in view of Lin et al. (WO 99/49879). The basis for this rejection is set forth at pages 12-15 of the previous Office Action of 16 August 2010 and page 10-13 of the Office Action of 06 January 2010.

Hilton et al. identify a new family of proteins (SOCS) which are capable of acting as regulators of signaling (column 3, lines 27-30). Hilton et al. teach an isolated nucleic acid sequence that encodes the SOCS3 amino acid sequence of SEQ ID NO: 4 of the instant application (see nucleic acids 18-692 of SEQ ID NO:7 of Hilton et al.; see also sequence

alignment attached to the Office Action of 06 January 2010 as Appendix A). Hilton et al. also disclose nucleic acid molecules encoding other members of the SOCS family, as well as the proteins themselves (column 3, lines 58-59; column 7, lines 33-52; column 10, Table 1). Hilton et al. disclose a pharmaceutical composition comprising genetic molecules, such as a vector capable of transfecting target cells where the vector carries a nucleic acid molecule capable of modulating SOCS expression or SOCS activity (column 31, lines 65-67 through column 32, lines 1-6). Hilton et al. teach the use of SOCS or its functional derivatives in the manufacture of a medicament for the treatment of conditions involving cytokine mediated cellular responsiveness (column 36, lines 8-11).

Hilton et al. do not teach a polypeptide comprising a SOCS sequence and a membrane translocation sequence. Hilton et al. do not teach a nucleic acid encoding a polypeptide comprising a SOCS sequence and a membrane translocation sequence.

Lin et al. teach a membrane translocating sequence (MTS) for directing import of biologically active protein molecules into a cell, and a method of using an expression vector in a host cell to produce a fusion protein comprising a membrane-translocating sequence and a biologically active polypeptide (page 1, 2nd paragraph). Lin et al. disclose that until now, DNA constructs, including DNA vaccines and recombinant viral vectors, have provided the most effective method for furnishing a protein product to the cell for processing and expression (page 2, line 32 through page 3, lines 1-3). Lin et al. add that the FDA has expressed concern about approval of DNA vaccines and that recombinant viral vectors have posed problems in terms of delivery into cells, efficiency of expression, and potential immune system response to viral proteins (page 3, lines 4-11). Lin et al. indicate that there is need for a method for importing

entire protein molecules into a cell for studies of intracellular processes in living systems, for drug delivery, for vaccine development, and for disease therapy (page 3, lines 22-25). Lin et al. teach an artificial MTS sequence of 12 amino acids (and DNA encoding such) that can be used as a fusion with a target protein for import into the cell (page 7, lines 23-29). The MTS of Lin et al. is 100% identical to the amino acid sequence of SEQ ID NO: 2 of the instant application (see page 7, lines 31-32 of Lin et al.; SEQ ID NO: 1 of Lin et al.). Lin et al. disclose that an expression vector comprising the MTS and the target protein may also encode a polyhistidine (6xHis) sequence and an epitope tag to allow rapid purification of the fusion protein (page 13, lines 29 through page 14, lines 1-5).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the SOCS amino acid sequences (and nucleic acid sequences encoding such) of Hilton et al. by fusing them to a membrane translocation sequence as taught by Lin et al. The person of ordinary skill in the art would have been motivated to make that modification because (i) SOCS proteins are *intracellular* regulators of cell signaling, wherein modulation of SOCS activity or expression requires administration of agonists, antagonists, or DNA constructs as taught by Hilton et al. and (2) problems with DNA constructs (i.e., gene therapy and recombinant viral vectors) were known in the art at the time the invention was made (see Lin et al. page 3, lines 4-11). The person of ordinary skill in the art reasonably would have expected success because Lin et al. demonstrate the successful import of target proteins into a cell using a membrane translocation sequence (page 38, last example; also, pages 35-37). Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

Applicants' arguments (16 February 2011), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At the top of page 9 of the Response, Applicants argue that out of the exceedingly large number of intracellular proteins that are known, the different types of membrane penetrating sequences that are available, would require unlimited and undue experimentation without the teachings of the instant invention. Applicants assert that neither of the references provide any reasoning as to why these two particular proteins should be brought together in the manner taught by Applicants. Applicants add that since SOCS function as intracellular signaling proteins with a very short half-life, one of skill in the art would not have been motivated to combine Hilton et al. with Lin et al. to import a protein with a very short half-life into a cell as such a treatment would require a constant administration to a patient.

Applicants' arguments have been fully considered but are not found to be persuasive. Applicant is reminded that the instant rejection is a rejection under 35 U.S.C. § 103(a) and not under 35 U.S.C. § 112, first paragraph (enablement). Furthermore, when the reference(s) relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference(s) is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. See MPEP §2121(I) and *In re Sasse*, 629 F.2d 675, 207 USPQ 107 (CCPA 1980).

In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references

themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, Hilton et al. teach that SOCS proteins are intracellular regulators of cell signaling, wherein modulation of SOCS activity or expression requires administration of agonists, antagonists, or DNA constructs (column 3, lines 27-30; column 31, lines 65-67 through column 32, lines 1-6). Hilton et al. teach the use of SOCS or its functional derivatives in the manufacture of a medicament for the treatment of conditions involving cytokine mediated cellular responsiveness (column 36, lines 8-11). It was well known in the prior art that SOCS proteins are intracellular (see for example, Larsen et al. (APMIS 110: 833-844, 2002;; Figure 4), and Lin et al. teach that problems with DNA constructs (such as gene therapy and recombinant viral vectors) were known in the art at the time the invention was made and could be overcome by fusing an artificial membrane translocating sequence to a target protein for import into the cell (page 3, lines 4-11; page 7, lines 23-29).

Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the SOCS amino acid sequences (and nucleic acid sequences encoding such) of Hilton et al. by fusing them to a membrane translocation sequence as taught by Lin et al. The person of ordinary skill in the art would have been motivated to make that modification because (i) SOCS proteins are *intracellular* regulators of cell signaling, wherein modulation of SOCS activity or expression for the treatment of conditions involving cytokine mediated cellular responsiveness requires administration of agonists, antagonists, or DNA constructs as taught by Hilton et al. and (2) problems with DNA constructs (i.e., gene therapy

and recombinant viral vectors) were known in the art at the time the invention was made (see Lin et al. page 3, lines 4-11).

(ii) At the middle of page 9 of the Response of 16 February 2011, Applicants submit that neither of these references provide any guidance or teachings to engineer the actual proteins disclosed in the instant application. Applicants contend that the engineered proteins of the instant specification provide for controlled delivery of SOCS for the replacement of depleted stores of intracellular physiologic protein, a feasible alternative to gene transfer. Applicants state that they have been able to provide for the controlled delivery of the SOCS protein resulting in one of skill in the art to be able to correctly dose the amount of SOCS needed for therapy. Applicants argue that one of skill in the art would not conceive of importing protein with a very short half-life, especially in view of the fact that it would not be feasible nor provide the ability to control the amounts of SOCS in the target cell.

Applicants' arguments have been fully considered but are not found to be persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Hilton et al. teach an isolated nucleic acid sequence that encodes the SOCS3 amino acid sequence of SEQ ID NO: 4 of the instant application (see nucleic acids 18-692 of SEQ ID NO:7 of Hilton et al.; see also sequence alignment attached to the Office Action of 06 January 2010 as Appendix A). Hilton et al. also disclose nucleic acid molecules encoding other members of the SOCS family, as well as the

proteins themselves (column 3, lines 58-59; column 7, lines 33-52; column 10, Table 1). Hilton et al. disclose a pharmaceutical composition comprising genetic molecules, such as a vector capable of transfecting target cells where the vector carries a nucleic acid molecule capable of modulating SOCS expression or SOCS activity (column 31, lines 65-67 through column 32, lines 1-6). Hilton et al. teach the use of SOCS or its functional derivatives in the manufacture of a medicament for the treatment of conditions involving cytokine mediated cellular responsiveness (column 36, lines 8-11). Although Hilton et al. do not teach a polypeptide or polynucleotide comprising a SOCS sequence and a membrane translocation sequence, Lin et al. teach a membrane translocating sequence (MTS) for directing import of biologically active protein molecules into a cell, and a method of using an expression vector in a host cell to produce a fusion protein comprising a membrane-translocating sequence and a biologically active polypeptide (page 1, 2nd paragraph). Lin et al. disclose that until now, DNA constructs, including DNA vaccines and recombinant viral vectors, have provided the most effective method for furnishing a protein product to the cell for processing and expression (page 2, line 32 through page 3, lines 1-3). Lin et al. teach an artificial MTS sequence of 12 amino acids (and DNA encoding such) that can be used as a fusion with a target protein for import into the cell (page 7, lines 23-29). The MTS of Lin et al. is 100% identical to the amino acid sequence of SEQ ID NO: 2 of the instant application (see page 7, lines 31-32 of Lin et al.; SEQ ID NO: 1 of Lin et al.). Additionally, Lin et al. teaches methods for genetically engineering a protein with a membrane translocating sequence (see pages 10-19; 30-37).

In response to applicant's argument that one of skill in the art would not conceive of importing protein with a very short half-life, especially in view of the fact that it would not be

feasible nor provide the ability to control the amounts of SOCS in the target cell, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

6. Claims 12, 13, 14, 23, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shouda et al. (J Clin Invest 108(12): 1781-1788, 2001) in view of Hilton et al. (U.S. Patent 6,323,317) and Lin et al. (WO 99/49879). The basis for this rejection is set forth at pages 15-17 of the previous Office Action of 16 August 2010 and at pages 13-16 of the Office Action of 06 January 2010.

Shouda et al. teach that the mRNA of SOCS3 (CIS3) is abundantly expressed in patients with rheumatoid arthritis, an autoimmune disease characterized by chronic inflammation of the joints (abstract; page 1783, column 2; page 1784, column 1). Shouda et al. teach that the administration of a recombinant adenovirus carrying SOCS3 cDNA is injected into the ankle joints of mice with antigen-induced arthritis or collagen-induced arthritis (abstract; bottom of page 1784, column 2; page 1785 through page 1786). Shouda et al. disclose that the SOCS3 adenovirus drastically reduced the severity of arthritis and joint swelling as compared to controls (abstract; Figures 5, 6; page 1787, column 1, second full paragraph). Shouda et al. conclude that adenovirus-mediated gene transfer of the SOCS3 gene is a promising means of treatment for rheumatoid arthritis (abstract; page 1788, top of column 1).

Shouda et al. do not teach the administration of a polypeptide comprising a SOCS sequence and a membrane translocation sequence.

Hilton et al. identify a new family of proteins (SOCS) which are capable of acting as regulators of signaling (column 3, lines 27-30). Hilton et al. teach an isolated nucleic acid sequence that encodes the SOCS3 amino acid sequence of SEQ ID NO: 4 of the instant application (see nucleic acids 18-692 of SEQ ID NO:7 of Hilton et al.; see also sequence alignment attached to the Office Action of 06 January 2010 as Appendix A). Hilton et al. also disclose nucleic acid molecules encoding other members of the SOCS family, as well as the proteins themselves (column 3, lines 58-59; column 7, lines 33-52; column 10, Table 1). Hilton et al. disclose a pharmaceutical composition comprising genetic molecules, such as a vector capable of transfecting target cells where the vector carries a nucleic acid molecule capable of modulating SOCS expression or SOCS activity (column 31, lines 65-67 through column 32, lines 1-6). Hilton et al. teach the use of SOCS or its functional derivatives in the manufacture of a medicament for the treatment of conditions involving cytokine mediated cellular responsiveness (column 36, lines 8-11).

Lin et al. teach a membrane translocating sequence (MTS) for directing import of biologically active protein molecules into a cell, and a method of using an expression vector in a host cell to produce a fusion protein comprising a membrane-translocating sequence and a biologically active polypeptide (page 1, 2nd paragraph). Lin et al. disclose that until now, DNA constructs, including DNA vaccines and recombinant viral vectors, have provided the most effective method for furnishing a protein product to the cell for processing and expression (page 2, line 32 through page 3, lines 1-3). Lin et al. add that the FDA has expressed concern about approval of DNA vaccines and that recombinant viral vectors have posed problems in terms of delivery into cells, efficiency of expression, and potential immune system response to viral

proteins (page 3, lines 4-11). Lin et al. indicate that there is need for a method for importing entire protein molecules into a cell for studies of intracellular processes in living systems, for drug delivery, for vaccine development, and for disease therapy (page 3, lines 22-25). Lin et al. teach an artificial MTS sequence of 12 amino acids (and DNA encoding such) that can be used as a fusion with a target protein for import into the cell (page 7, lines 23-29). The MTS of Lin et al. is 100% identical to the amino acid sequence of SEQ ID NO: 2 of the instant application (see page 7, lines 31-32 of Lin et al.; SEQ ID NO: 1 of Lin et al.). Lin et al. disclose that an expression vector comprising the MTS and the target protein may also encode a polyhistidine (6xHis) sequence and an epitope tag to allow rapid purification of the fusion protein (page 13, lines 29 through page 14, lines 1-5).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of treating rheumatoid arthritis of Shouda et al. by substituting the recombinant adenovirus carrying SOCS3 cDNA for a fusion polypeptide comprising SOCS3 and a membrane translocation sequence as taught by Hilton et al. and Lin et al. The person of ordinary skill in the art would have been motivated to make that modification because problems with DNA constructs (i.e., gene therapy and recombinant viral vectors) were known in the art at the time the invention was made (see Lin et al. page 3, lines 4-11). The person of ordinary skill in the art reasonably would have expected success because Lin et al. demonstrate the successful import of target proteins into a cell using a membrane translocation sequence (page 38, last example; also, pages 35-37). Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

Applicants' arguments (16 February 2011), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicants assert that it would not be obvious to one of ordinary skill in the art to combine SOCS and MTS, including the Shouda et al. study. Applicants contend that since SOCS has a very short half-life, and assuming arguendo, that one of ordinary skill in the art did combine Hilton et al. and Lin et al., one of skill in the art would rather incorporate SOCS in an expression vector so as to prevent the degradation of SOCS until the expression vector containing the SOCS nucleic acid sequence was in the cell. Applicants also state that with Shouda et al., further describing the use of vectors to express proteins, one of skill in the art would be taught away from using a protein with a very short half-life in the treatment of inflammatory diseases. Applicants submit that rather one of skill in the art would be directed to a vector expressing such a SOCS protein. Applicants argue that neither Hilton et al. in view of Lin et al. provide the necessary motivation to combine the SOCS and MTS as taught by Applicants.

Applicants arguments have been fully considered but are not found to be persuasive. In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case,

Shouda et al. teach that SOCS3 adenovirus reduces the severity of arthritis and joint swelling and conclude that adenovirus-mediated gene transfer of the SOCS3 gene is a promising means of treatment (abstract; Figures 5, 6; page 1787, column 1, second full paragraph; page 1788, top of column 1); and Lin et al. teach that problems with DNA constructs (such as gene therapy and recombinant viral vectors) were known in the art at the time the invention was made and could be overcome by fusing an artificial membrane translocating sequence to a target protein for import into the cell (page 3, lines 4-11; page 7, lines 23-29).

Furthermore, contrary to Applicants arguments, one of skill in the art would not be taught away from using a SOCS protein in the treatment of inflammatory diseases. Shouda et al. disclose that the SOCS3 adenovirus drastically reduces the severity of arthritis and joint swelling as compared to controls (abstract; Figures 5, 6; page 1787, column 1, second full paragraph). Shouda et al. conclude that adenovirus-mediated gene transfer of the SOCS3 gene is a promising means of treatment for rheumatoid arthritis (abstract; page 1788, top of column 1). Additionally, Hilton et al. teach the use of SOCS or its functional derivatives in the manufacture of a medicament for the treatment of conditions involving cytokine mediated cellular responsiveness (column 36, lines 8-11). Lin et al. teach a membrane translocating sequence (MTS) for directing import of biologically active protein molecules into a cell. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of treating rheumatoid arthritis of Shouda et al. by substituting the recombinant adenovirus carrying SOCS3 cDNA for a fusion polypeptide comprising SOCS3 and a membrane translocation sequence as taught by Hilton et al. and Lin et al.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571)272-0881. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
01 July 2011

/Bridget E Bunner/
Primary Examiner, Art Unit 1647